(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 May 2001 (25.05.2001)

PCT

(10) International Publication Number
WO 01/36421 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/519, A61P 7/02 // (C07D 487/04, 249:00, 239:00)

(21) International Application Number: PCT/SE00/02229

(22) International Filing Date:
14 November 2000 (14.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9904129-5 15 November 1999 (15.11.1999) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/36421 A1

(54) Title: NOVEL [1,2,3]-TRIAZOLO[4,5-D]PYRIMIDINE COMPOUNDS

(57) Abstract: The invention provides novel [1,2,3]-triazolo[4,5-d]pyrimidine analogue compounds of formula (I), their use as medicaments, compositions containing them and processes for their preparation.

NOVEL [1,2,3]-TRIAZOLO[4,5-D]PYRIMIDINE COMPOUNDS

FIELD OF THE INVENTION

The present invention provides novel [1,2,3]-triazolo[4,5-d]pyrimidine analogues, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

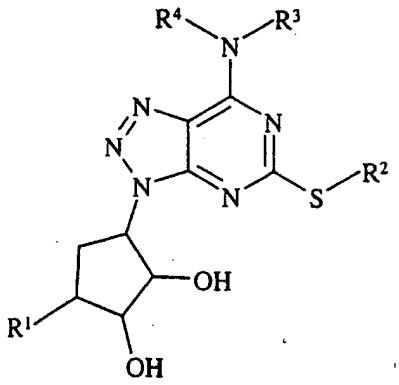
Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and platelet-mediated occlusion or re-occlusion also compromises angioplasty.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K. L. et. al. (1994) *Circulation* **90**, pp. 1638-1642).

It has been found that adenosine 5'-diphosphate (ADP) acts as a key mediator of thrombosis. ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology*, (1994), **113**, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) **124**, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) **42**, 213). There is a need to find P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

DESCRIPTION OF THE INVENTION

In a first aspect the invention provides a compound of formula (I):



(I)

wherein:

R^1 is OR^5 or CH_2R^6;

R^2 is alkyl C_{1-6} or haloalkyl C_{1-6};

R^3 is cycloalkyl C_{3-6}, optionally substituted by R^7;

R^4 is alkyl C_{1-6};

R^5 is H or alkyl C_{1-6}, optionally substituted by OH;

R^6 is OH, N_3, or NHR^8;

R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, and OR^{10};

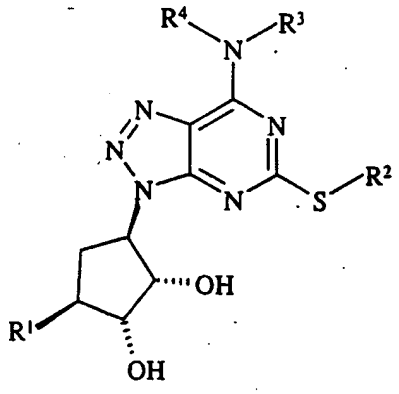
R^8 is H, alkyl C_{1-6}, or COR^9;

R^9 is alkyl C_{1-6};

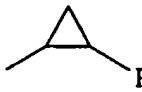
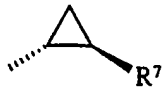
R^{10} is alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

Preferably the compound of formula (I) has the following stereochemistry:



(Ia)

Where R^3 is  R^7 the stereochemistry is preferably 

Suitably R^1 is OH, $O(CH_2)_2OH$, CH_2OH, CH_2N_3, CH_2NH_2, or CH_2NHAc.

Suitably R^2 is n-Pr.

Suitably R^3 is cyclopropyl optionally substituted with phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen and OR^{10}.

Suitably R^4 is methyl.

Particularly preferred compounds of the invention include:

[1*S*-[1α,2α,3β,5β(1*S**, 2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**, 2*R**)]]-4-[7-[*N*-Methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-(Hydroxymethyl)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[7-[*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[7-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-Azidomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-*3H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

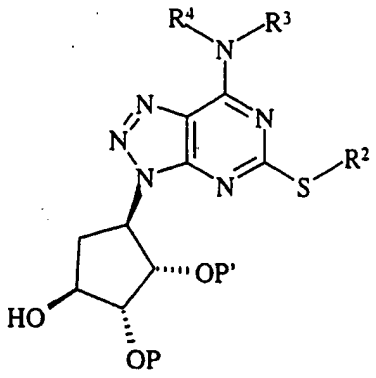
[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-Aminomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*R*-[1α,2β,3β,4α(1*R**,2*S**)]]-*N*-[[2,3-Dihydroxy-4-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentyl]methyl]acetamide;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:

a. For compounds of formula (I) where R^1 is $O(CH_2)_2OH$, the reaction of a compound of formula (II)



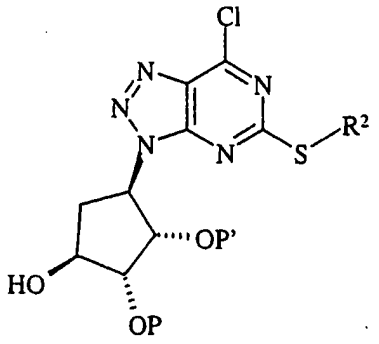
(II)

where R^2, R^3 and R^4 are defined in formula (I), P and P' are protecting groups, for example CMe_2, with 2-(2-bromoethoxy)-2*H*-tetrahydropyran, in the presence of dimethylsulphoxide and a phase transfer catalyst, such as a tetra-alkylammonium halide, preferably tetra-butylammonium bromide, and aqueous sodium hydroxide, in the presence of a water-immiscible organic solvent, preferably toluene, at a temperature of between about 50 and about 120°C, and optionally thereafter removing any protecting groups.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Tetrahydropyranyl groups can be removed by the use of an acid, for example, trifluoroacetic acid, in water or aqueous acetonitrile, at a temperature between about 20 and about 50°C.

A compound of formula (II) can be prepared by reacting a compound of formula (III)

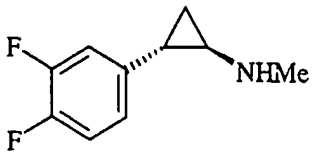
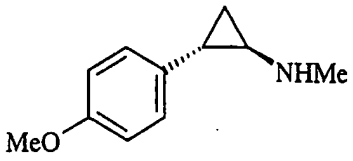


(III)

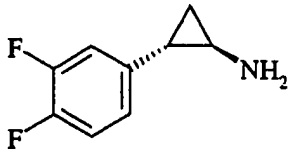
where P, P', R^2 are defined above, with R^3R^4NH, in the presence of a base, preferably N,N-di-isopropylethylamine, in an inert ethereal solvent, preferably diethyl ether or tetrahydrofuran or a chlorocarbon solvent, preferably dichloromethane, at a temperature of between about 20 and about 50°C.

Where R^3R^4NH is  and R^7 is phenyl, the compound may be prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, *27*, 768-773, using (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044).

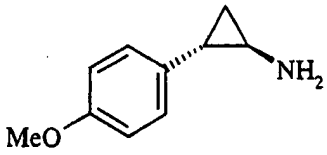
Where R^3R^4NH is

 or 

such compounds can be prepared by acylation of

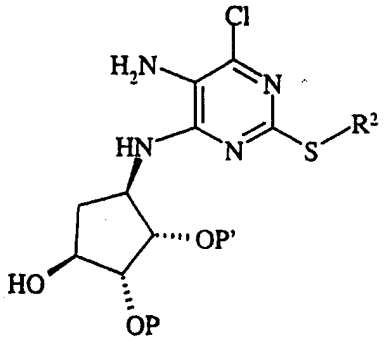


or



(prepared as described in International Patent Application WO 9905143) with acetic anhydride and potassium carbonate in tetrahydrofuran, at a temperature of between about 20 and about 50°C. The product of this reaction can be methylated with sodium hydride and methyl iodide in tetrahydrofuran, at a temperature of between about 20 and about 50°C, followed by deacylation with aqueous hydrochloric acid, at a temperature of between about 20 and about 100°C

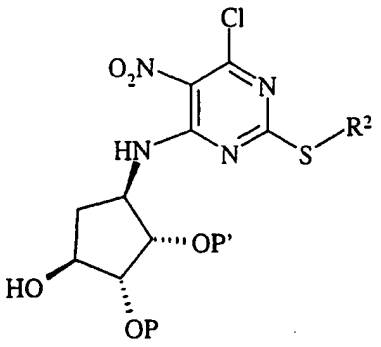
A compound of formula (III) can be prepared by diazotising a compound of formula (IV)



(IV)

where P, P' and R^2 are defined above, with an alkyl nitrite, preferably iso-amylnitrite, in an inert dipolar aprotic solvent, preferably acetonitrile, at a temperature between about 50 and about 100°C.

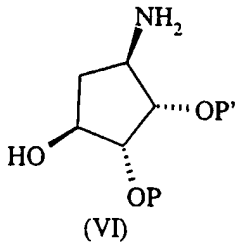
A compound of formula (IV) can be prepared by reducing a compound of formula (V),



(V)

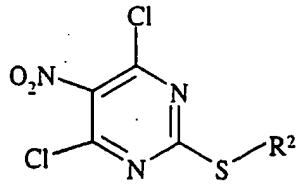
where P, P' and R^2 are defined above, using a metal, preferably iron powder, in the presence of an acid, preferably acetic acid, at a temperature between about 20 and about 50°C.

A compound of formula (V) can be prepared by reacting a compound of formula (VI),



(VI)

where P and P' are defined above, with a compound of formula (VII):

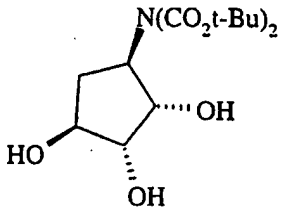


(VII)

where R^2 is defined above, in the presence of a base, preferably *N,N*-di-isopropylethylamine, in an inert ethereal solvent, preferably tetrahydrofuran, at a temperature between about 20 and about 50°C.

Where R^2 is n-Pr, the compound of formula (VII) can be prepared as described in International Patent Application WO 9703084.

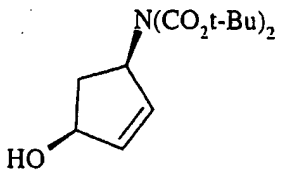
A compound of formula (VI) can be prepared by reacting a compound of formula (VIII),



(VIII)

with a ketal or acetal, preferably 2,2-dimethoxypropane, in acetone as solvent, in the presence of an acid, preferably *p*-toluenesulphonic acid, at a temperature of between about 20 and about 50°C, followed by hydrolysis and decarboxylation of the protected iminodiester under aqueous conditions, preferably in water, at a temperature of between about 100 and about 120°C.

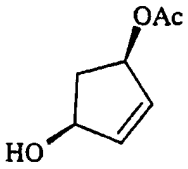
A compound of formula (VIII) can be prepared by dihydroxylating a compound of formula (IX),



(IX)

using osmium tetroxide, in the presence of an oxidising agent, preferably *N*-methylmorpholine-*N*-oxide, under aqueous conditions, preferably in aqueous tetrahydrofuran, at a temperature between about 20 and about 50°C.

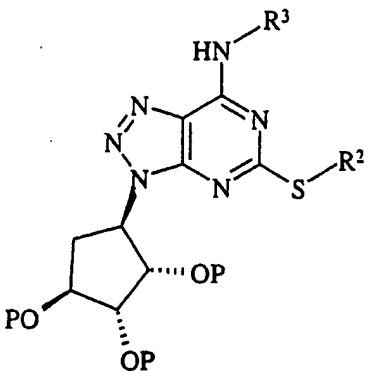
A compound of formula (IX) can be prepared by reacting a compound of formula (X):



(X)

with a protected amine, preferably imidodicarbonic acid bis-(1,1-dimethylethyl)ester, in the presence of a base, preferably sodium hydride, and an organometallic catalyst, preferably tetrakis(triphenylphosphine)palladium(0), in an inert ethereal solvent, preferably tetrahydrofuran, at a temperature between about 20 and about 100°C.

b. For compounds of formula (I) where R^1 is OH, reacting a compound of formula (XI):

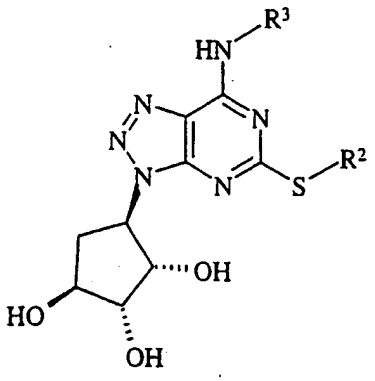


(XI)

where P is a protecting group and R^2 and R^3 are defined above, with a base, preferably sodium hydride, and an alkylating agent, preferably methyl iodide, in an inert dipolar aprotic solvent preferably *N,N*-dimethylformamide, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups

Protecting groups include trialkylsilyl groups, preferably the *t*-butyldimethylsilyl group. This can be removed by reaction with a tetraalkylammonium fluoride, preferably tetrabutylammonium fluoride, under aqueous conditions, preferably aqueous tetrahydrofuran, at a temperature between about 20 and about 50°C.

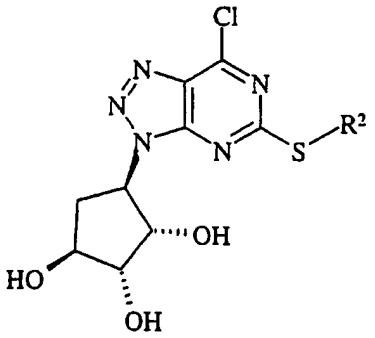
A compound of formula (XI) can be made by reacting a compound of formula (XII):



(XII)

where R^2 and R^3 are defined above, with a trialkylsilylhalide, preferably *t*-butyldimethylsilylchloride, in the presence of imidazole, in an inert dipolar aprotic solvent, preferably N,N-dimethylformamide, at a temperature between about 20 and about 50°C.

A compound of formula (XII) can be made by reacting a compound of formula (XIII):

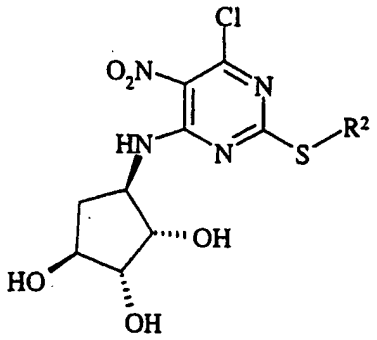


(XIII)

where R^2 is as defined in formula (I), with an amine R^3NH_2, in the presence of a base, preferably *N,N*-di-isopropylethylamine, in an inert ethereal solvent, preferably diethyl ether or tetrahydrofuran, at a temperature between about 20 and about 50°C.

Where R^3NH_2 is (1*R-trans*)-2-phenylcyclopropanamine, (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) it may be prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044.

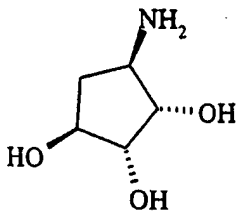
A compound of formula (XIII) can be made by reducing a compound of formula (XIV),



(XIV)

where R^2 is defined above, in the presence of a metal, preferably iron powder, and an acid, preferably acetic acid, at a temperature between about 20 and about 50°C, followed by diazotisation of the aminopyrimidine using an alkylnitrite, preferably iso-amylnitrite, in an inert dipolar aprotic solvent, preferably acetonitrile, at a temperature between about 50 and about 100°C.

A compound of formula (XIV) can be prepared by reacting a compound of formula (VII) with a compound of formula (XV)

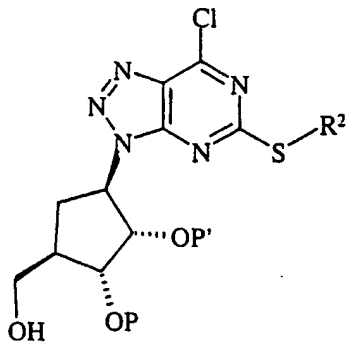


(XV)

in the presence of a base, preferably triethylamine or *N,N*-di- isopropylethylamine, in an inert ethereal solvent, preferably tetrahydrofuran, at a temperature between about 20 and about 100 °C.

Compounds of formula (XV) can be prepared by the hydrolysis and decarboxylation of a compound of formula (VIII) using the methods described in step a.

c. For compounds of formula (I) where R^1 is CH_2OH the reaction of a compound of formula (XVI)



(XVI)

where R^2 is defined in formula (I), P and P' are protecting groups, with R^3R^4NH and a base, preferably *N,N*-di-isopropylethylamine, in a chlorocarbon solvent, preferably dichloromethane, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

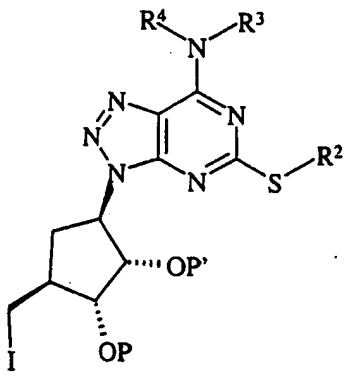
The preparation of R^3R^4NH is described above.

Where P and P' are CMe_2, the protecting groups can be removed using an acid under aqueous conditions, preferably using aqueous hydrochloric acid or aqueous trifluoroacetic

acid in an alcoholic solvent, preferably methanol at a temperature between about 20 and about 50°C.

The preparation of a compound of formula (XVI), where P and P' are CMe_2, is described in International Patent Application WO 9703084.

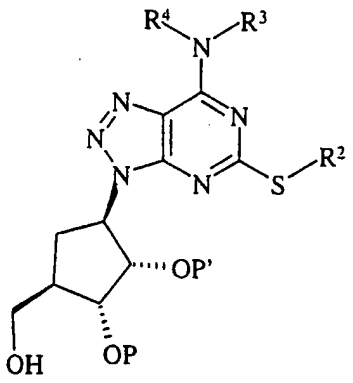
d. For compounds of formula (I) where R^1 is CH_2N_3, the reaction of a compound of formula (XVII)



(XVII)

where R^2, R^3 and R^4 are defined in formula (I), and P and P' are protecting groups, with an alkali metal azide, preferably sodium azide, in an inert chlorocarbon solvent, preferably dichloromethane, at a temperature between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

A compound of formula (XVII) can be made by reaction of a compound of formula (XVIII)



(XVIII)

where R^2, R^3 and R^4 are defined in formula (I), P and P' are protecting groups, with an iodinating agent, preferably methyltriphenoxyphosphonium iodide, in an inert chlorocarbon solvent, preferably dichloromethane, at a temperature between about 20 and about 50°C.

Compound (XVIII) can be prepared using the methods described in steps a-c.

e. For compounds of formula (I) where R^1 is CH_2NH_2, reduction of a compound of formula (I) where R^1 is CH_2N_3 (synthesised as described in step d), with hydrogen, in the presence of a transition metal catalyst, preferably10% palladium on carbon, in an inert alcoholic solvent, preferably ethanol, at a temperature between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

f. For compounds of formula (I) where R^1 is CH_2NHCOR^9, where R^9 is defined above, acylation of a compound of formula (I) where R^1 is CH_2NH_2 (synthesised as described in step e), with an acylating agent, preferably an acid anhydride $(R^9CO)_2O$, in the presence of a base, preferably *N,N*-diisopropylethylamine, in an inert chlorocarbon solvent, preferably dichloromethane, at a temperature between about 20 and about 50°C, followed by treatment with an alkali metal alkoxide, preferably sodium methoxide, in an alcoholic solvent, preferably methanol, at a temperature between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

Compounds of formulae (II), (XVII), and (XVIII) form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary revascularisation procedures including angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced

platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina. The invention also provides a method of treatment or prevention of the above disorders which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to the invention.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres, which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the person. With this system the active compound with or without a carrier substance is delivered to the person.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or

amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution, which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2))

was carried out using Fisher Matrix silica, 35-70 μm. For examples which showed the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[1*S*-[1α,2α,3β,5β(1*S, 2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol**

a) (1*R*-*cis*)-Bis(1,1-dimethylethyl)-4-hydroxy-2-cyclopentenylimidodicarbonate

Imidodicarbonic acid bis-(1,1-dimethylethyl) ester (25.0 g) was added to a suspension of ether-washed sodium hydride (3.94g of a 60% dispersion in oil) in tetrahydrofuran (500 ml). The mixture was stirred at 50°C for 2 hours. (1*S*-*cis*)-4-acetoxy-2-cyclopenten-1-ol (10.0 g) and tetrakis(triphenylphosphine)palladium (0) (2.0 g) was added to the reaction mixture, at ambient temperature. The reaction mixture was stirred for 24 hours diluted with water and extracted with ethyl acetate. The organic extracts were dried, concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate: hexane 1:5 as eluant) to give the sub-title compound as a solid (20.0 g).

NMR δH (d_6-DMSO) 5.71-5.77 (2H, m), 4.91 (1H, d, J = 5.4 Hz), 4.86 (1H, tq, J = 8.0, 1.8), 4.51-4.57 (1H, m), Hz), 2.54 (1H, dt, J = 12.6, 7.4 Hz), 1.61 (1H, ddd, J = 12.3, 7.7, 6.4 Hz), 1.43 (18H, s).

b) [1*R*-(1α,2β,3β,4α)]-2,3,4-Trihydroxycyclopentenylimidodicarbonic acid, bis(1,1-dimethylethyl) ester

N-methylmorpholine-*N*-oxide (11.08 g) was added to a solution of the product of step a) (20.0 g) in tetrahydrofuran (500 ml) and water (50 ml). Subsequently osmium tetroxide (11.75 ml, 2.5% solution in *t*-butanol) was added and the mixture was stirred at room

temperature overnight then treated with sodium hydrosulphite (6.0 g). The suspension was filtered through Celite and the solid residue washed with methanol. The filtrate was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate: hexane 1:1 as eluant) to afford the sub-title compound (17.37 g).

NMR δH (d_6-DMSO) 4.82 (1H, d, J = 4.6 Hz), 4.56 (1H, d, J = 5.9 Hz), 4.54 (1H, d, J = 4.8 Hz), 4.11-4.21 (2H, m), 3.66-3.73 (1H, m), 3.55-3.58 (1H, m), 1.97-2.05 (1H, m), 1.46-1.60 (1H, m), 1.44 (18H, s).

c) [3a*R*-(3aα,4α,6α,6aα)]-6-Amino-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol

p-Toluenesulphonic acid (0.86 g) was added to a solution of the product of step b) (15.0 g) in acetone (250 ml) containing 2,2-dimethoxypropane (22.1 ml). The mixture was stirred at ambient temperature for 30 minutes. The mixture was partitioned between ethyl acetate (700 ml) and brine (300 ml) and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Water (250 ml) was added water to the residual gum and the mixture heated at reflux for 24 hours. The cooled reaction mixture was concentrated *in vacuo* and dried by azeotropic distillation with toluene to provide sub-title compound (7.5 g).

MS (APCI) 174 ($M+H^+$, 100%).

d) [3a*R*-(3aα,4α,6α,6aα)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol

A solution of the product of step c) (7.5 g) in tetrahydrofuran (500 ml) was added over 1 hour to a solution of 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine (prepared as described in International Patent Application WO 9703084) (25.57 g) and *N*,*N*-diisopropylethylamine (8.3 ml) in tetrahydrofuran (1000 ml) and stirred for a further 1 hour. The reaction mixture was concentrated *in vacuo*, ethyl acetate added (1000 ml) and the mixture was washed with water. The organic layer was dried ($MgSO_4$), evaporated and the residue purified by

chromatography (SiO_2, isohexane-ethyl acetate as eluant) to afford the sub-title compound (14.22 g).

MS (APCI) 405/7 ($M+H^+$), 405 (100%).

e) [3a*R*-(3aα,4α,6α,6aα)]-6-[[5-Amino-6-chloro-2-propylthiopyrimidin-4-yl]amino]-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol

Iron powder (15.0 g) was added to a stirred solution of the product of step d) (13.45 g) in acetic acid (500 ml). The reaction mixture was stirred at room temperature for 2 hours and concentrated to half volume *in vacuo*. The residue was diluted with ethyl acetate and the mixture washed with water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the sub-title compound (10.26 g).

MS (APCI) 375/7 ($M+H^+$), 375 (100%).

f) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]-pyrimidin-3-yl]-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol

Isoamyl nitrite (5.5 ml) was added to a solution of the product of step e) (10.26 g) in acetonitrile (500 ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate:isohexane 2:1 as eluant) to afford the sub-title compound (8.93 g).

MS (APCI) 386/8 ($M+H^+$), 386 (100%).

g) [3a*R*-[3aα,4α,6α(1*R, 2*S**),6aα]]-Tetrahydro-2,2-dimethyl-6-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxol-4-ol**

A mixture of the product of step f) (1.0 g), (1*R-trans*)-*N*-methyl-2-phenylcyclopropanamine hydrochloride (prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, *27*, 768-773, using (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044) (0.522 g) and *N,N*-diisopropylethylamine (1.35 ml) in ether (20 ml) was stirred at room temperature for 2 hours. The reaction mixture was washed successively with 1M hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the sub-title compound (1.23 g).

MS (APCI) 497 ($M+H^+$, 100%).

h) [3a*S*-[3aα,4α(1*S,2*R**),6α,6aα]-*N*-Methyl-*N*-(2-phenylcyclopropyl)-3-[[[[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]oxy]-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine.**

Aqueous NaOH (5N, 10 ml) was added to a solution of the product of step g) (1.23 g) in toluene (10 ml). Subsequently, tetrabutylammonium bromide (0.12 g) was added and the mixture stirred for 30 minutes. Dimethyl sulfoxide (704 µl) and 2-(2-bromoethoxy)-2*H*-tetrahydropyran (3.93 ml) were added and the reaction mixture was heated at reflux for 16 hours. Further 2-(2-bromoethoxy)-2*H*-tetrahydropyran (3.93 ml) and tetrabutylammonium bromide (0.12 g) were added and the reaction mixture was heated at reflux for 16 hours. The reaction mixture was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate: hexane 1:4 as eluant) to afford the sub-title compound (1.2 g).

MS (APCI) 625 ($M+H^+$, 100%).

i) [1*S*-[1α,2α,3β,5β(1*S, 2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol**

A solution of the product of step h) (0.50 g) in trifluoroacetic acid (9 ml) and water (1 ml) was stirred at room temperature for 1 hour then concentrated *in vacuo* and the residue purified by chromatography (HPLC, Novapak® C18 column, 0.1% aqueous ammonium acetate:acetonitrile, 55:45) to afford the title compound (0.113 g).

MS (APCI) 501 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.31-6.87 (5H, m), 4.98 (1H, q, J = 8.5 Hz), 4.81 (1H, d, J = 6.5 Hz), 4.73 (1H, d, J = 4.1 Hz), 4.61-4.56 (1H, m), 4.29 (1H, br s), 4.00-3.97 (1H, m), 3.83-3.79 (1H, m), 3.56-3.49 (7H, m), 3.08-3.01 (2H, m), 2.98-2.91 (1H, m), 2.66-2.58 (1H, m), 2.41 (1H, m), 2.10-2.03 (1H, m), 1.63 (1H, sextet, J = 7.2 Hz), 1.58-1.53 (1H, m), 1.45 (1H, q, J = 6.6 Hz), 0.94 (3H, t, J = 7.2 Hz).

Example 2

[1*S*-[1α,2β,3β,4α(1*S, 2*R**)]]-4-[7-[*N*-Methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

a) [1*S*-(1α,2β,3β,4α)]-[4-[6-Chloro-5-nitro-2-(propylthio)pyrimidin-4-yl]amino]cyclopentane-1,2,3-triol

2M hydrochloric acid (5 ml) was added to a solution of the product of Example 1, step b) (0.6 g) in methanol (10 ml). The mixture was stirred for 24 hours, concentrated *in vacuo* and dried by azeotropic distillation with toluene. A solution of 4,6-dichloro-5-nitro-2-(propylthio)-pyrimidine (prepared as described in International Patent Application WO 9703084) (0.82 g) in tetrahydrofuran (5 ml) was added to a suspension of the residual amine hydrochloride and *N*,*N*-diisopropylethylamine (1.78 ml) in tetrahydrofuran (10 ml). The mixture was heated at reflux for 24 hours, cooled, concentrated *in vacuo* and the residue purified by chromatography (SiO_2, isohexane-ethyl acetate 3:7 as eluant) to afford the sub-title compound (0.469 g).

MS (APCI) 365/7 ($M+H^+$), 365 (100%).

b) [1*S*-(1α,2β,3β,4α)]-[4-[5-Amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino]cyclopentane-1,2,3-triol

The sub-title compound was prepared according to the method of Example 1, step e) using the product of step a) and was used directly in the next step.

c) [1*S*-(1α,2β,3β,4α)]-4-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol

The sub-title compound was prepared according to the method of Example 1, step f) using the product of step b).

MS (APCI) 346/8 ($M+H^+$), 346 (100%).

d) [1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

The sub-title compound was prepared according to the method of Example 1, step g) using the product of step c) and (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044).

MS (APCI) 443 ($M+H^+$,100%).

e) [1*R*-[1α(1*R,2*S**),2β,3β,4α]]-*N*-(2-Phenylcyclopropyl)-5-(propylthio)-3-[2,3,4-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclopentyl]-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine**

A mixture of the product of step d) (1.79 g), *tert*-butyldimethylsilylchloride (1.22 g) and imidazole (1.10 g) in *N,N*-dimethylformamide (3 ml) was stirred at ambient temperature for 24 hours. Further *tert*-butyldimethylsilylchloride (1.0 g) was added and the mixture stirred for a further 6 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate: hexane 1:20 as eluant) to afford the sub-title compound (2.43 g).

NMR δH ($CDCl_3$) 7.34-7.18 (5H, m), 6.38 and 3.22 (1H, br s), 5.30-5.19 (1H, m), 4.96-4.89 (1H, m), 4.04-3.99 (1H, m), 3.89-3.86 (1H, m), 3.11-3.01 (2H, m), 2.83-2.70 (1H, m), 2.24-2.16 (1H, m), 2.14-2.03 (1H, m), 1.75-1.61 (2H, m), 1.5-1.3 (2H, m), 0.98-0.92 (3H, m), 0.94 (9H, s), 0.93 (9H, s), 0.69 (9H, s), 0.13 (3H, s), 0.12 (3H, s), 0.09 (3H, s), 0.08 (3H, s), -0.19 (3H, s), -0.47 (3H, s).

f) [1*R*-[1α(1*R,2*S**),2β,3β,4α]]-*N*-Methyl-*N*-(2-phenylcyclopropyl)-5-(propylthio)- 3-[2,3,4-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclopentyl]-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine**

Sodium hydride (35mg of a 60% dispersion in oil) was added to a solution of the product of step e) (0.576 g) in tetrahydrofuran (10 ml). The solution was stirred at ambient temperature for 30 minutes and methyl iodide (68 µl) was added. After 5 hours further methyl iodide (68 µl) was added and stirring was continued for 36 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate: hexane 1:20 as eluant) to afford the sub-title compound (0.537 g).

NMR δH ($CDCl_3$) 7.35-7.18 (5H, m), 5.32-5.22 (1H, m), 4.89 (1H, dd, J = 8.3, 3.3 Hz), 4.03 (1H, dt, J = 6.5, 1.7 Hz), 3.91-3.87 (1H, m), 4.4-3.6 (3H, br s), 3.12-3.02 (2H, m), 2.82-2.70 (1H, m), 2.38-2.26 (1H, m), 2.17-2.05 (1H, m), 1.80-1.65 (2H, m), 1.48-1.40 (1H, m), 1.27-0.65 (5H, m), 0.95 (9H, s), 0.93 (9H, s), 0.69 (9H, s), 0.13 (3H, s), 0.12 (3H, s), 0.09 (3H, s), 0.08 (3H, s), -0.19 (3H, s), -0.45 (3H, s).

g) [1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

Tetrabutylammonium fluoride (1M in tetrahydrofuran/water 95/5; 2.3 ml) was added to a solution of the product of step f) (0.53 g) in tetrahydrofuran (10 ml). The solution was stirred at ambient temperature for 20 hours, concentrated *in vacuo* and the residue purified by chromatography (HPLC, Novapak® C18 column, 0.1% aqueous ammonium acetate:acetonitrile) to afford the title compound (0.23 g).

MS (APCI) 457 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.32-7.18 (5H, m), 4.97 (1H, q, *J*=8.5 Hz), 4.91 (1H, d, *J*=4.5 Hz), 4.77 (1H, d, *J*=6.5 Hz), 4.68-4.63 (2H, m), 3.97-3.95 (1H, m), 3.82 (1H, m), 3.57 (3H, br s), 3.15-2.90 (3H, m), 2.63-2.33 (2H, m), 1.97-1.93 (1H, m), 1.63-1.54 (3H, m), 1.45-1.43 (1H, m), 0.93 (3H, t, *J*=7.0 Hz).

Example 3

[1*S*-[1α,2α,3β,5β(1*S,2*R**)]]-3-(Hydroxymethyl)-5-[7-[*N*-methyl-2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol**

a) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-Tetrahydro-2,2-dimethyl-6-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-methanol**

N,*N*-Diisopropylethylamine (2 ml) was added to a solution of [3a*R*-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084) (1.15 g) and (1*R*-*trans*)-*N*-methyl-2-phenylcyclopropanamine hydrochloride (prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, *27*, 768-773,

using (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044)) (0.53 g) in dichloromethane (20 ml). The reaction mixture was stirred at room temperature for 18 hours, then washed with water, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ethyl acetate:isohexane 1:1 as eluent) to afford the sub-title compound (1.3 g).

MS (APCI) 511 ($M+H^+$, 100%).

b) [1*S*-[1α,2α,3β,5β(1*S,2*R**)]]-3-(Hydroxymethyl)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol**

A solution of the product from step a) (0.25 g) in methanol (8 ml) and 2N HCl (2 ml) was stirred at room temperature for 3 hours and then concentrated *in vacuo*. The residue was tritrurated with acetonitrile (5 ml) to yield a white solid which was collected by filtration. Tritruration with methanol (5 ml) afforded the title compound (0.19 g).

MS (APCI) 471 ($M+H^+$, 100%).

NMR δH (d_6-DMSO at 90°C) 7.33-7.20 (5H, m), 5.02 (1H, q), 4.46 (1H, q), 3.93 (1H, q), 3.59-3.46 (5H, m), 3.08-2.98 (3H, m), 2.44-2.40 (1H, m), 2.31-2.24 (1H, m), 2.18-2.12 (1H, m), 1.92-1.85 (1H, m), 1.68-1.53 (3H, m), 1.44 (1H, q), 0.95 (3H, t).

Example 4

[1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[7-[*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

a) (1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]acetamide

Acetic anhydride (0.31 ml) was added to a suspension of (1*R-trans)*-2-(3,4-difluorophenyl)cyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described in International Patent Application WO 9905143) (700mg) and potassium carbonate (1.0 g) in tetrahydrofuran (20 ml) and stirred for 20 h. Saturated ammonium chloride solution was added and the mixture was extracted with ether and the organic layers were dried ($MgSO_4$) and evaporated to afford the sub-title compound (470mg).

MS (APCI) 270 ($M+MeCO_2^-$, 100%).

b) (1*R-trans*)-*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-*N*-methylacetamide

Sodium hydride (109mg of a 60% dispersion in oil) was added to a solution of the product from step a) (470 mg) and methyl iodide (0.4 ml) in tetrahydrofuran (15 ml) and stirred for 18h. Saturated ammonium chloride solution was added and the mixture was extracted with ether. The organic layers were dried ($MgSO_4$), evaporated and purified by chromatography (SiO_2, dichloromethane:methanol (49:1) as eluant) to give the sub-title compound (470 mg).

MS (APCI) 226 ($M+H^+$, 100%).

c) (1R-*trans*)-2-(3,4-Difluorophenyl)-*N*-methylcyclopropanamine, hydrochloride

A solution of the product from step b) (443 mg) in 4M HCl (10 ml) was refluxed for 8h. The solvent was removed *in vacuo* to give the sub-title compound (357 mg).

NMR δH (d_6-DMSO) 9.25 (1H, s), 7.39-7.30 (2H, m), 7.09-7.02 (1H, m), 2.98-2.95 (1H, m), 2.64 (3H, s), 1.52-1.51 (1H, m), 1.31-1.29 (2H, m).

d) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-Tetrahydro-2,2-dimethyl-6-[7-[*N*-[2-(3,4-difluorophenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-ol**

The sub-title compound (800 mg) was prepared according to the method of Example 3, step a) from the product of Example 1, step f) (612 mg) and the product from step c) (357 mg).

MS (APCI) 533 ($M+H^+$, 100%).

e) [1*S*-[1α,2β,3β,4α(1*S, 2*R**)]]-4-[7-[*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

A solution of the product from step a) (798 mg) in a mixture of trifluoroacetic acid (8 ml), methanol (5 ml) and water (3 ml) was stirred at room temperature for 1 hour, poured into 2M potassium carbonate and extracted with ethyl acetate. The extract was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, dichloromethane:methanol (14:1) as eluant) to afford the title compound (703 mg).

MS (APCI) 493 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.40-7.30 (2H, m), 7.15-7.03 (1H, m), 5.12 (1H, dd), 5.03-4.95 (2H, m), 4.93 (1H, d), 4.68 (1H, q), 3.98-3.55 (3H, m), 3.10-2.90 (1H, m), 2.85-2.72 (1H, m), 2.64-2.54 (1H, m), 2.40-2.20 (1H, m), 1.97-1.85 (1H, m), 1.80-1.42 (4H, m), 1.02-0.82 (3H, m).

Example 5

[1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[7-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

a) **(1*R*-*trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]acetamide**

The sub-title compound was prepared according to the method of Example 4, step a) from (1*R*-*trans*)-2-(4-methoxyphenyl)cyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described in WO9905143) to give a white solid (655 mg).

MS (APCI) 206 ($M+H^+$, 100%).

b) **(1*R*-*trans*)-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-*N*-methylacetamide**

The sub-title compound was prepared according to the method of Example 4, step b) using the product from step a) to afford a white solid (587 mg).

MS (APCI) 220 ($M+H^+$, 100%).

c) **(1R-*trans*)-2-(4-Methoxyphenyl)-*N*-methylcyclopropanamine, hydrochloride**

The sub-title compound was prepared according to method of Example 4, step c) from the product of step b) to afford a white solid (507 mg).

NMR δH (d_6-DMSO) 9.24 (2H, s), 7.11-7.09 (2H, m), 6.87-6.85 (2H, m), 3.72 (3H, s), 2.88-2.84 (1H, m), 2.64 (3H, s), 2.44-2.39 (1H, m), 1.46-1.41 (1H, m), 1.97-1.15 (1H, m).

d) **[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[7-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

The title compound (400 mg) was prepared according to the method of Example 3, step a) from the product of Example 1, step f) (765 mg) and the product from step c) (507 mg); followed by deprotection using the method of Example 4, step e).

MS (APCI) 487 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.20-7.17 (2H, m), 6.88-6.85 (2H, m), 4.98-4.96 (1H, q), 4.69-4.65 (1H, m), 3.98-3.97 (1H, m), 3.85-3.82 (1H, m), 3.74 (3H, s), 3.56 (3H, s), 3.55-3.41 (4H, m), 3.07-2.99 (2H, m), 2.50-2.48 (1H, m), 2.47-2.38 (1H, m), 2.00-1.96 (1H, m), 1.68-1.61 (2H, m), 1.50-1.47 (1H, m), 1.38-1.36 (1H, m), 0.97-0.92 (3H, t).

Example 6

[1S-[1α,2α,3β,5β(1S*,2R*)]]-3-Azidomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol

a) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-*N*-Methyl-*N*-(2-phenylcyclopropyl)-5-(propylthio)-3-[tetrahydro-6-(iodomethyl)-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]- 3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-amine

A solution of the product from Example 3a) (1.0 g) in dichloromethane (10 ml) was treated with methyltriphenoxyphosphonium iodide (1.5 g) and the resultant solution was left to stand for 30 minutes at room temperature. This mixture was then purified by chromatography (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the sub-title compound (0.77 g).

MS (APCI) 621 ($M+H^+$, 100%).

b) [1S-[1α,2α,3β,5β(1S*,2R*)]]-3-Iodomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol

A solution of the product from step a) (0.76 g) in a mixture of tetrahydrofuran (6 ml) and methanol (4 ml) was treated with 2 molar aqueous hydrochloric acid (1.5 ml) and the solution allowed to stand at 35°C for 5 hours. The mixture was concentrated *in vacuo* and the residue was azeotroped with toluene (3 x 100 ml). The residue was purified by chromatography (SiO_2, ethyl acetate:isohexane 1:2 as eluant) to afford the sub-title compound (0.53 g).

MS (APCI) 581 ($M+H^+$, 100%).

c) [1S-[1α,2α,3β,5β (1S*,2R*)]]-3-Azidomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2-diol

A solution of the product from step b) (0.53 g) in dimethyl sulphoxide (5 ml) was treated with sodium azide (0.07 g) and the resultant mixture was stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate (200 ml) and a saturated solution of aqueous brine (200 ml). The ethyl acetate layer was washed with water (3 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (0.43 g).

MS (APCI) 496 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.32-7.19 (5H, m), 5.01 (1H, q), 4.81 (1H, d), 4.63 (1H, d), 4.41 (1H, q), 3.91 (1H, q), 3.60-3.49 (2H, m), 3.06-2.98 (6H, m), 2.45-2.35 (2H, m), 2.30-2.20 (1H, m), 1.91-1.86 (1H, m), 1.67-1.52 (3H, m), 1.45-1.42 (1H, m), 0.94 (3H, t).

Example 7

[1S-[1α,2α,3β,5β(1S*,2R*)]]-3-Aminomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol, hydrochloride salt

A solution of the product from Example 6, step c) (0.39 g) in ethanol (15 ml) was treated with 10% palladium on carbon catalyst (0.04 g) and the resultant mixture was stirred vigorously under 4 atmospheres of hydrogen for 4 hours. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in 1,4-dioxane (10 ml) and then treated with a slight excess of concentrated hydrochloric acid. The solution was concentrated *in vacuo* and the residue azeotroped with toluene (3 x 100 ml) before being tritrurated with ethyl acetate to afford the title compound (0.16 g).

MS (APCI) 470 ($M+H^+$, 100%).

NMR δH (d_6-DMSO at 90°C) 8.00 (3H, s), 7.33-7.17 (5H, m), 5.03-4.96 (1H, m), 4.37 (1H, t), 4.01 (1H, t), 3.56 (3H, s), 3.10-2.93 (4H, m), 2.45-2.35 (2H, m), 1.90-1.79 (1H, m), 1.67-1.53 (3H, m), 1.44 (1H, q), 0.94 (3H, t).

Example 8

[1R-[1α,2β,3β,4α(1R*,2S*)]]-*N*-[2,3-Dihydroxy-4-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-*3H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentylmethyl]acetamide

A solution of the product from Example 7 (0.2 g) in dichloromethane (15 ml) was treated with *N,N*-diisopropylethylamine (0.11 g) followed by acetic anhydride (0.16 g) and the resultant mixture was stirred at room temperature for 4 hours. The mixture was washed with a saturated solution of aqueous sodium bicarbonate (15 ml) and the organic layer concentrated *in vacuo*. The residue was dissolved in a 0.1 molar solution of sodium methoxide in methanol (20 ml) and the solution allowed to stand for 2 hours at room temperature. Following concentration *in vacuo* the residue was acidified by careful addition

of acetic acid, the mixture was again concentrated *in vacuo* and he residue azeotroped with toluene (3 x 100 ml). Purification by chromatography (SiO_2, methanol:chloroform 1:24 as eluant) gave the title compound (0.12 g).

MS (APCI) 512.5 ($M+H^+$, 100%).

NMR δH (d_6-DMSO at 90°C) 7.63 (1H, s), 7.32-7.19 (5H, m), 4.98 (1H, q), 4.72 (1H, d), 4.48-4.44 (2H, m), 3.86 (1H, q), 3.34-3.29 (1H, m), 3.12-3.06 (1H, m), 3.05-2.97 (5H, m), 2.42-2.39 (1H, m), 2.37-2.30 (1H, m), 2.20-2.15 (1H, m), 1.81-1.75 (4H, m), 1.67-1.52 (3H, m), 1.44 (1H, q), 0.94 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal

function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows

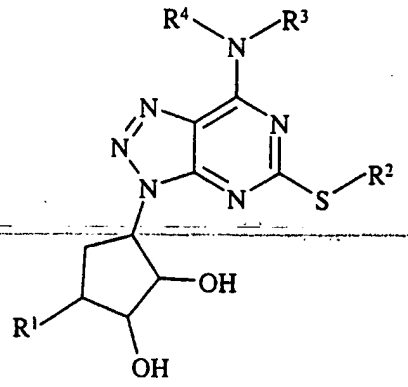
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX was used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to estabiish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is OR^5 or CH_2R^6;

R^2 is alkyl C_{1-6} or haloalkyl C_{1-6};

R^3 is cycloalkyl C_{3-6}, optionally substituted by R^7;

R^4 is alkyl C_{1-6};

R^5 is H or alkyl C_{1-6}, optionally substituted by OH;

R^6 is OH, N_3, or NHR^8;

R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, and OR^{10};

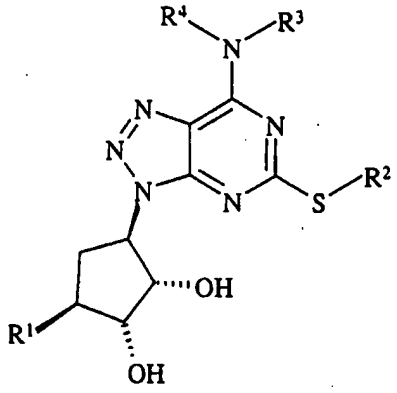
R^8 is H, alkyl C_{1-6}, or COR^9;

R^9 is alkyl C_{1-6};

R^{10} is alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

2. A compound according to claim 1 which is:



(Ia)

where R^1, R^2, R^3 and R^4 are as defined in claim 1.

3. A compound according to claim 2 in which R^3 is  where R^7 is as defined in claim 1.

4. A compound according to any one of claims 1 to 3, in which R^1 is OH, $O(CH_2)_2OH$, CH_2OH, CH_2N_3, CH_2NH_2 or CH_2NHAc.

5. A compound according to any one of claims 1 to 4, in which R^2 is n-Pr.

6. A compound according to any one of claims 1 to 5, in which R^3 is cyclopropyl optionally substituted with phenyl.

7. A compound according to claim 6 in which R^3 is cyclopropyl substituted with phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen and OR^{10}.

8. A compound according to any one of claims 1 to 7 in which R^4 is methyl.

9. A compound according to claim 1 which is:

[1*S*-[1α,2α,3β,5β(1*S**, 2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**, 2*R**)]]-4-[7-[*N*-Methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-(Hydroxymethyl)-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[7-[*N*-[2-(3,4-Difluorophenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[7-*N*-[2-(4-Methoxyphenyl)cyclopropyl]-*N*-methylamino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-Azidomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-*3H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-Aminomethyl-5-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2-diol;

[1*R*-[1α,2β,3β,4α(1*R**,2*S**)]]-*N*-[[2,3-Dihydroxy-4-[7-[*N*-methyl-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]cyclopentyl]methyl]acetamide;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

11. A pharmaceutical composition for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, comprising a compound according to any one of claims 1 to 9.

12. A pharmaceutical composition for use in the treatment or prevention of unstable or stable angina, comprising a compound according to any one of claims 1 to 9.

13. A compound according to any one of claims 1 to 9 for use in therapy.

14. A compound according to any one of claims 1 to 9 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

15. A compound according to any one of claims 1 to 9 for use in the treatment or prevention of unstable or stable angina.

16. The use of a compound according to any one of claims 1 to 9 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

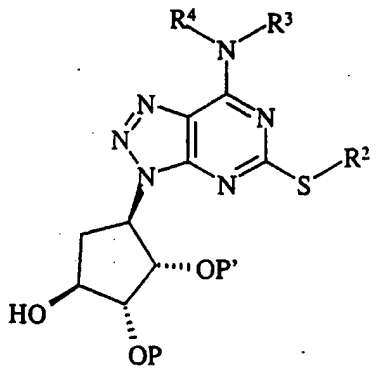
17. The use of a compound according to any one of claims 1 to 9 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of unstable or stable angina

18. A method of treatment or prevention of a platelet aggregation disorder which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 9.

19. A method of treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a condition a therapeutically effective amount of a compound according to any one of claims 1 to 9.

20. A method of treatment or prevention of unstable or stable angina which comprises administering to a person suffering from or susceptible to such a condition a therapeutically effective amount of a compound according to any one of claims 1 to 9.

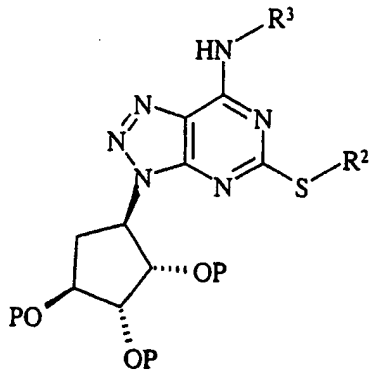
21. A process for the preparation of a compound of formula (I) where R^1 is $O(CH_2)_2OH$, which comprises reacting a compound of formula (II):



(II)

where R^2, R^3 and R^4 are as defined in claim 1, P and P' are protecting groups, with 2-(2-bromoethoxy)-2*H*-tetrahydropyran, in the presence of dimethylsulphoxide, a phase transfer catalyst, aqueous sodium hydroxide and a water-immiscible organic solvent,at a temperature of between about 50 and about 120°C, and optionally thereafter removing any protecting groups.

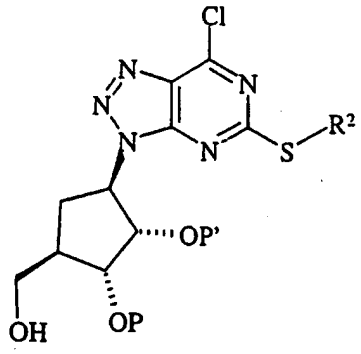
22. A process for the preparation of a compound of formula (I) where R^1 is OH, which comprises reacting a compound of formula (XI):



(XI)

where P is a protecting group and R^2 and R^3 are as defined in claim 1, with as base and an alkylating agent, in an inert dipolar aprotic solvent, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

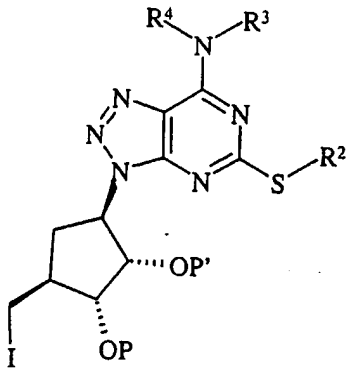
23. A process for the preparation of a compound of formula (I) where R^1 is CH_2OH, which comprises reacting a compound of formula (XVI):



(XVI)

where R^2 is as defined in claim 1, P and P' are protecting groups, with R^3R^4NH and a base in a chlorocarbon solvent, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

24. A process for the preparation of a compound of formula (I) where R^1 is CH_2N_3, which comprises reacting a compound of formula (XVII):



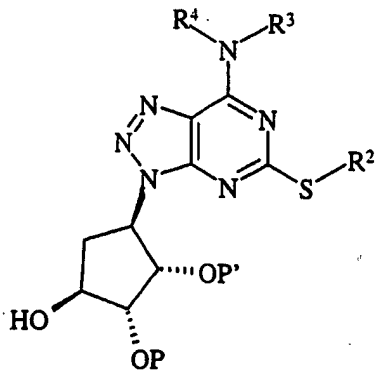
(XVII)

where R^2, R^3 and R^4 are as defined in claim 1 and P and P' are protecting groups, with an alkali metal azide, in an inert chlorocarbon solvent, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

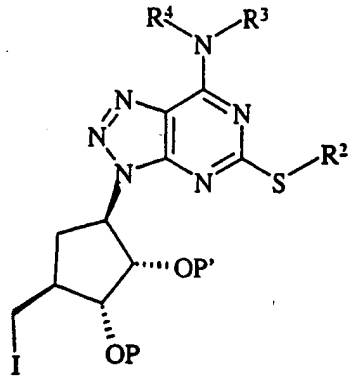
25. A process for the preparation of a compound of formula (I) where R^1 is CH_2NH_2, which comprises reducing a compound of formula (I) synthesised as described in claim 24, with hydrogen, in the presence of a transition metal catalyst, in an inert alcoholic solvent, at a temperature of between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

26. A process for the preparation of a compound of formula (I) where R^1 is CH_2NHCOR^9, which comprises acylating a compound of formula (I) synthesised as described in claim 25, with an acylating agent, in the presence of a base, in an inert chlorocarbon solvent, at a temperature between about 20 and about 50°C, followed by treatment with an alkali metal alkoxide, in an alcoholic solvent, at a temperature between about 20 and about 50°C, and optionally thereafter removing any protecting groups.

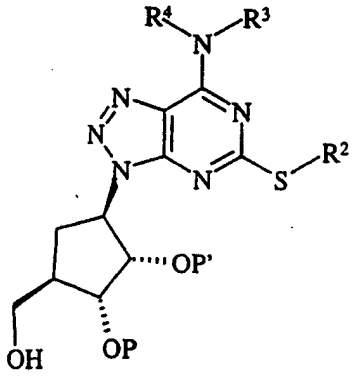
27. Compounds of formulae (II), (XVII), and (XVIII);



(II)



(XVII)



(XVIII)

where R^2, R^3 and R^4 are defined in claim 1, and P and P' are protecting groups.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02229

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 487/04, A61K 31/519, A61P 7/02 // (C07D 487/04, 249:00, 239:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9905142 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99)	1-27
X	WO 9828300 A1 (ASTRA PHARMACEUTICALS LTD.), 2 July 1998 (02.07.98)	1-27
X	WO 9941254 A1 (ASTRA PHARAMCEUTICALS LTD.), 19 August 1999 (19.08.99)	1-27
P,A	WO 0004021 A1 (ASTRA PHARMACEUTICALS LTD.), 27 January 2000 (27.01.00)	1-27

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	08 -02- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02229

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02229

Claims 18-20 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02229

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9905142 A1	04/02/99	AU 8370598 A	16/02/99
		BR 9811022 A	12/09/00
		CN 1271359 T	25/10/00
		EP 0996620 A	03/05/00
		NO 20000311 A	21/03/00
		SE 9702772 D	00/00/00
WO 9828300 A1	02/07/98	AU 5501598 A	17/07/98
		EP 0946561 A	06/10/99
		SE 9604787 D	00/00/00
		SE 9604788 D	00/00/00
WO 9941254 A1	19/08/99	AU 723699 B	07/09/00
		AU 2650099 A	30/08/99
		AU 6430498 A	12/10/98
		BR 9811253 A	26/09/00
		BR 9907934 A	24/10/00
		EP 1017439 A	12/07/00
		EP 1056749 A	06/12/00
		NO 994433 A	13/09/99
		NO 20004089 A	16/10/00
		PL 335701 A	08/05/00
		SE 9800458 D	00/00/00
		SE 9803669 D	00/00/00
WO 0004021 A1	27/01/00	AU 5539899 A	07/02/00
		SE 9802574 D	00/00/00